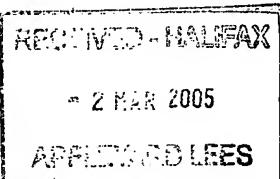


PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WALSH, David, Patrick
Appleyards Lees
15 Clare Road
Halifax HX1 2HY
GRANDE BRETAGNE



PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	28.02.2005
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Applicant's or agent's file reference
DPW/Y1912 blue

IMPORTANT NOTIFICATION

International application No. PCT/GB 03/04679	International filing date (day/month/year) 31.10.2003	Priority date (day/month/year) 30.11.2002
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Applicant
LUCITE INTERNATIONAL UK LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/I/B/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

30/5/05 - add Patents?

Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Roche, S Tel. +49 89 2399-8031
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DPW/Y1912	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 03/04679	International filing date (day/month/year) 31.10.2003	Priority date (day/month/year) 30.11.2002
International Patent Classification (IPC) or both national classification and IPC C07C67/347		
Applicant LUCITE INTERNATIONAL UK LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.
3. This report contains indications relating to the following items:
 - I Basis of the opinion
 - II Priority
 - III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV Lack of unity of invention
 - V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI Certain documents cited
 - VII Certain defects in the international application
 - VIII Certain observations on the international application

Date of submission of the demand 30.06.2004	Date of completion of this report 28.02.2005
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seelmann, M Telephone No. +49 89 2399-8335



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB 03/04679

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-38 as originally filed

Claims, Numbers

1-28 filed with telefax on 30.12.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB 03/04679

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1,2,5(part)-23(part), 25, 26(part)-28(part)
	No:	Claims	3,4,5(part)-23(part),24, 26(part)-28(part)
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB 03/04679

Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1 EP 0 495 548 cited in the present application
- D2 WO 01 68 583 cited in the present application
- D3 US 4 377 708
- D4 US 4 500 727

V.1 Amendments - Art.34(2)b) PCT

Present claims 1 and 2 corresponds to old claims 2 and 7. By doing these modifications, the applicant introduced a clarity problem: basically the second step in order to produce lactate ester is missing in present claim 1; formula (I) should have been introduced in claim 1 and removed from claim 3 and the part "in accordance with the first aspect as defined herein" should have been deleted.

Such changes in numbering does not have any influence on Art.34(2)b) PCT.

V.2 Novelty - Art. 33(2) PCT

Carbonylation of vinyl acetate is known from D1 to lead to a (40:60) linear: branched acetoxy-propionates ratio working in presence of palladiumacetate and 1,3-bis(di-tert.butylphosphino)propane as catalytic system (example XII in tables I and II).

The catalytic system comprising a metal group VIII and a bidentate phosphine of formula (I) as already been used in D2 for the carbonylation of substituted ethylenically unsaturated compounds including for instance carboxy group(s) (page 8, lines 1-7), in particular exemplified is methyl-3-pentenoate (page 8, line 16). No mention of vinyl acetate as a starting material or further use of such a step in the synthesis of methyl lactate.

D3 and D4 both refer to the production of methyl lactate in a multiple step pathway starting from vinyl acetate. D3 describes the hydrocarboxylation of vinyl acetate with tertiary organophosphine stabilized palladium catalysts followed by hydrolysis of the acetoxypropionic intermediates to produce lactic acid. D4 relates to the hydroformylation of vinyl acetate in

presence of a rhodium complex and tri-substituted phosphine, followed by oxydation of the acetoxy-aldehydes to the corresponding acids and methanolysis to recover methyl lactate by distillation.

None of the above-cited documents pertain to the production of acetoxy-propionates from vinyl acetate in the presence of a catalytic system comprising a metal of group VIII and a bidentate phosphine of formula (I) according to claim 1 or further use of such a step in the production of methyl lactate. Novelty is accordingly recognized for the subject-matters of claims 1 to 28.

V.3 Inventive step - Art. 33(3) PCT

3.1 Production of lactate ester

Production of lactate ester from vinyl acetate is known D4 via hydroformylation and oxidation. The technical problem posed is to provide another method of preparing the lactate ester of acid (II). The proposed solution is the production of mostly the branched acetoxy-propionate as key intermediate from vinyl acetate by carbonylation using a catalytic system comprising a metal of group VIIIB and a bidentate phosphine of general formula (I) (claim 1). The proposed process has been proven to be solution to the technical problem (examples 1-6, tables 1-3, pages 32-35 in combination with preparation on page 37), since under such catalytic conditions the branched intermediate is mostly favored. But the catalytic system of D1 is already solution of such a technical problem, since in example XII the branched acetoxy-propionate is recovered in a ratio of 60 to 40 over the linear compound. The objective technical problem is accordingly a simple alternative, i.e. improving the experimental conditions to increase the preponderance of the branched compound. The proposed solution is the use of another bidentate phosphine, i.e. one of formula (I). Such a phosphine of formula (I) has been used already in the carbonylation of internally unsaturated esters producing in majority the linear product(D2, example 6, page 2, lines 18-25; comparison between D1 and D2 in D2, table 1 and page 10, lines 20-26). Accordingly the skilled person aware of both teachings would not have been inclined to combine them to come to the present solution. Accordingly an inventive step is recognized for the process according to claims 1, 24 and dependent thereof in view of D1/D2 and D4.

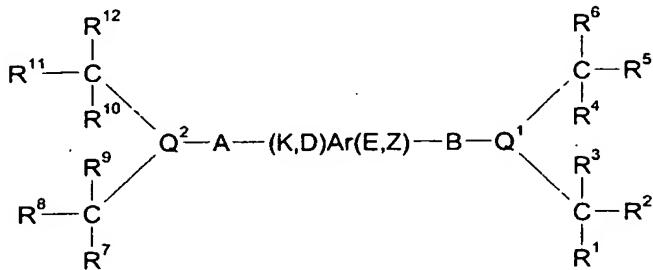
3.2 Carbonylation of vinyl acetate

CLAIMS

1. A process for the carbonylation of vinyl acetate comprising reacting vinyl acetate with carbon monoxide in the presence of a source of hydroxyl groups and of a catalyst system, the catalyst system obtainable by combining:

- 5 (a) a metal of Group VIII B or a compound thereof; and
- (b) a bidentate phosphine of general formula (I)

10 (I)



wherein:

Ar is a bridging group comprising an optionally substituted aryl moiety to which the phosphorus atoms are linked on available adjacent carbon atoms;

15 A and B each independently represent lower alkylene;

K, D, E and Z are substituents of the aryl moiety (Ar) and each independently represent hydrogen, lower alkyl, aryl, Het, halo, cyano, nitro, OR¹⁹, OC(O)R²⁰, C(O)R²¹, C(O)OR²², NR²³R²⁴, C(O)NR²⁵R²⁶, C(S)R²⁵R²⁶, SR²⁷, C(O)SR²⁷, or -J-Q³(CR¹³(R¹⁴)(R¹⁵))CR¹⁶(R¹⁷)(R¹⁸)

20 where J represents lower alkylene; or two adjacent groups selected from K, Z, D and E together with the carbon atoms of the aryl ring to which they are attached form a further phenyl ring, which is optionally substituted by one or more substituents selected from hydrogen, lower alkyl, halo, cyano, nitro, OR¹⁹, OC(O)R²⁰, C(O)R²¹, C(O)OR²², NR²³R²⁴, C(O)NR²⁵R²⁶, C(S)R²⁵R²⁶, SR²⁷ or C(O)SR²⁷ or, when Ar is a cyclopentadienyl group, Z may 25 be represented by -M(L₁)_n(L₂)_m and Z is connected via a metal ligand bond to the cyclopentadienyl group;

R¹ to R¹⁸ each independently represent lower alkyl, aryl, or Het;

30 R¹⁹ to R²⁷ each independently represent hydrogen, lower alkyl, aryl or Het;

M represents a Group VIB or VIIIB metal or metal cation thereof;

L₁ represents a cyclopentadienyl, indenyl or aryl group each of which groups are optionally substituted by one or more substituents selected from hydrogen, lower alkyl, halo, cyano, nitro, 5 OR¹⁹, OC(O)R²⁰, C(O)R²¹, C(O)OR²², NR²³R²⁴, C(O)NR²⁵R²⁶, C(S)R²⁵R²⁶, SR²⁷, C(O)SR²⁷ or ferrocenyl;

L₂ represents one or more ligands each of which are independently selected from hydrogen, lower alkyl, alkylaryl, halo, CO, PR⁴³R⁴⁴R⁴⁵ or NR⁴⁶R⁴⁷R⁴⁸;

10

R⁴³ to R⁴⁸ each independently represent hydrogen, lower alkyl, aryl or Het;

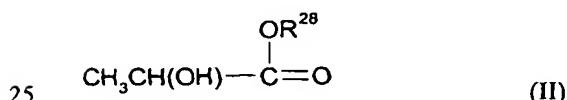
n = 0 or 1;

15 and m = 0 to 5;

provided that when n = 1 then m equals 0, and when n equals 0 then m does not equal 0;

Q¹, Q² and Q³ (when present) each independently represent phosphorous, arsenic or antimony 20 and in the latter two cases references to phosphine or phosphorous above are amended accordingly.

2. A process for the production of a lactate ester or acid of formula II



comprising the steps of carbonylating vinyl acetate with carbon monoxide in the presence of a source of hydroxyl groups and of a catalyst system, the catalyst system obtainable by combining:

30

- (a) a metal of Group VIII B or a compound thereof; and
- (b) a bidentate phosphine of general formula (I) in accordance with the first aspect as defined herein

to produce a product comprising a branched (iso) product 2-acetoxy (CH_3). $\text{CH}_2\text{C}(\text{O})\text{OR}^{28}$ wherein R^{28} is selected from H, or a $\text{C}_1\text{-C}_{30}$ alkyl or aryl moiety which may be substituted or unsubstituted and either branched or linear and chemically treating the said branched (iso) product to produce the corresponding lactate or acid of formula II.

5

3. A process for the production of 3-hydroxy propanoate ester or acid of formula (III)



10 comprising the steps of :

carbonylating vinyl acetate with carbon monoxide in the presence of a source of hydroxyl groups and of a catalyst system, the catalyst system obtainable by combining:

- (a) a metal of Group VIII B or a compound thereof; and
- 15 (b) a bidentate phosphine of general formula (I) in accordance with either claim 1 or claim 2 as defined above

wherein R^{28} is selected from H, or a $\text{C}_1\text{-C}_{30}$ alkyl or aryl moiety which may be substituted or unsubstituted and either branched or linear and carrying out a treatment step on the said linear
20 (n) product 1-acetoxy $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{OR}^{28}$ to produce the 3-hydroxy propanoate ester or acid of formula (III).

4. A process according to any preceding claim, wherein the Group VIII B metal is palladium.

25 5. A process according to any preceding claim, wherein the linear (n) and branched (iso) products of the carbonylation may be separated either before or after the treatment step.

6. A process according to any preceding claim, wherein the products of the reaction are separated by distillation.

30 7. A process according to any preceding claim, wherein the ratio of branched :linear product from the carbonylation process is greater than 1.5:1.

8. A process according to any preceding claim, wherein when K, D, E or Z represent -J-
35 $\text{Q}^3(\text{CR}^{13}(\text{R}^{14})(\text{R}^{15}))\text{CR}^{16}(\text{R}^{17})(\text{R}^{18})$, the respective K, D, E or Z is on the aryl carbon adjacent

the aryl carbon to which A or B is connected or, if not so adjacent, is adjacent a remaining K, D, E or Z group which itself represents -J-Q³(CR¹³(R¹⁴)(R¹⁵))CR¹⁶(R¹⁷)(R¹⁸).

9. A process according to any preceding claim, wherein the process is used to catalyse the
5 carbonylation of a vinyl acetate compound in the presence of carbon monoxide and a hydroxyl group containing compound.

10. A process according to any preceding claim, wherein the carbon monoxide may be used in pure form or diluted with an inert gas such as nitrogen, carbon dioxide or a noble gas such as
10 argon.

11. A process according to any preceding claim, wherein the ratio (volume/volume) of vinyl acetate compound to hydroxyl group containing compound lies in the range of 1:0.1 to 1:10.
15 12. A process according to any preceding claim, wherein the amount of Group VIII metal is in the range 10⁻⁷ to 10⁻¹ moles per mole of vinyl acetate compound.

13. A process according to any preceding claim, wherein the carbonylation of a vinyl acetate compound is performed in one or more aprotic solvents.
20

14. A process according to claim 13, wherein the aprotic solvent has a dielectric constant that is below 50 at 298.15 K and at 1x10⁵ Nm⁻².

15. A process according to any preceding claim, wherein the catalyst compounds act as a
25 heterogeneous catalyst.

16. A process according to any of claims 1 to 14, wherein the catalyst compounds act as a homogeneous catalyst.
30

17. A process according to claim 15 wherein the process is carried out with the catalyst comprising a support.

18. A process according to claim 17, wherein the support is insoluble.

19. A process according to either claim 17 or claim 18, wherein the support comprises a polymer such as a polyolefin, polystyrene or polystyrene copolymer such as a divinylbenzene copolymer or other suitable polymers or copolymers known to those skilled in the art; a silicon derivative such as a functionalised silica, a silicone or a silicone rubber; or other porous particulate material such as for example inorganic oxides and inorganic chlorides.
- 5
20. A process according to any preceding claim, wherein the carbonylation is carried out at a temperature of between -10 to 150°C.
- 10 21. A process according to any preceding claim, wherein the carbonylation is carried out at a CO partial pressure of between $0.80 \times 10^5 \text{ N.m}^{-2}$ - $90 \times 10^5 \text{ N.m}^{-2}$.
22. A process according to any of claims 1 to 20, wherein the carbonylation is carried out at a low CO partial pressure of between 0.1 to $5 \times 10^5 \text{ N.m}^{-2}$.
- 15 23. A process according to any preceding claim, wherein the bidentate phosphine is independently selected from any of the following: bis (di-t-butyl phosphino)-o-xylene (also known as 1,2 bis (di-t-butylphosphinomethyl) benzene); 1,2 bis (diadamantylphosphinomethyl) benzene; 1,2 bis (diadamantylphosphinomethyl) naphthalene;
- 20 1,2 bis (di-t-pentyl phosphino)-o-xylene (also known as 1,2 bis (di-t-pentyl-phosphinomethyl) benzene); bis 2,3 (di-t-butyl phosphinomethyl) naphthalene; 1,2-bis-(ditertbutylphosphinomethyl) ferrocene; 1,2,3-tris-(ditertbutylphosphinomethyl) ferrocene; 1,2 bis (diadamantylphosphinomethyl) ferrocene; and 1,2 bis (di-t-pentyl phosphinomethyl) ferrocene.
- 25 24. The use of the catalyst system according to any preceding claim for the production of a lactate ester or acid of formula (II) the said production comprising the steps of carbonylation of a vinyl acetate followed by treatment of the branched (iso) product of the carbonylation to produce the ester or acid.
- 30 25. The use of the catalyst system as defined in any of claims 1 to 23 for the production of a 3-hydroxy propanoate ester of formula (III) the said production comprising the steps of carbonylation of a vinyl acetate followed by treatment of the linear (n) product of the carbonylation.
- 35

26. The use of a catalyst system as defined in any of claims 1 to 23, wherein the catalyst is attached to a support.

27. The use of a catalyst according to either claim 24 or claim 25, wherein the treatment is
5 hydrolysis or transesterification.

28. The use of the catalyst according to claim 27, wherein the product is hydrogenated
subsequent to hydrolysis.

The closest related carbonylation of vinyl acetate is known from **D1** and differs from the present one by the bidentate phosphine used in the catalytic system, not falling under formula (I) of claim 1. The technical problem posed is to provide an alternative carbonylation. The proposed solution is the use of a catalytic system comprising a metal of group VIIIB and a bidentate phosphine of general formula (I) (claim 1). The proposed process has been proven to be solution to the technical problem (examples 1-6, tables 1-3, pages 32-35). Such a phosphine of formula (I) has been used already in the carbonylation of internally unsaturated esters (**D2**, example 6). The proposed solution corresponds therefore to the combination of the teachings of **D1** and **D2**, obvious alternative. No inventive step is accordingly recognized for the process according to claims 3-4, 25 and dependent thereof.

V.3 Further comments (Certain defects in the international application; Certain observations on the international application)

- a. The statement "lower" in claim 1 and paragraphs on page 37, line 24 - page 38, line 7 are vague and indefinite, contravening the requirements of clarity (PCT Guidelines CIII-4.3a and Article 6).
- b. The expression "incorporated by reference" contravenes to the PCT Guidelines CII-4.18.